16 December 2008

This supplement has been prepared to present scientific and technical news items that may be of more interest to technical personnel at RDT&E activities and the labs, or the medics rather than the broader readership of the basic CB Daily. Due to the nature of the material, the articles, if available online, are usually only available through subscription services thus making specific links generally unavailable. Thus, usually only the bibliographic citation is available for use by an activity's technical library.

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Chem-Bio News– Pandemic Influenza Edition # 40

1. U.S. HHS SUPPORTS INTERCELL'S DEVELOPMENT OF VACCINE PATCH SYSTEM FOR PANDEMIC INFLUENZA: *"Intercell is developing a Pandemic Influenza Vaccine Patch System that includes an immunostimulant patch administered in conjunction with an injected Pandemic Influenza vaccine (manufactured by Solvay Biologicals, B.V., The Netherlands); the system is designed to enhance the immune response and enable dose sparing of the Pandemic Influenza vaccine."*

2. PROGRESS REPORTED AT WHO MEETING ON VIRUS SHARING: *"Representatives from more than 100 countries participated in the negotiations, and the meeting was attended by a host of observers, nongovernmental organization representatives, and industry groups."*

3. GUIDANCE ON ANTIVIRAL DRUG USE DURING AN INFLUENZA PANDEMIC: *"The antiviral drug use guidance in this document replaces the recommendations developed in 2005 which are published as part of the Department of Health and Human Service's (HHS's) pandemic influenza plan.*

4. CONSIDERATIONS FOR ANTIVIRAL DRUG STOCKPILING BY EMPLOYERS IN PREPARATION FOR AN INFLUENZA PANDEMIC: *"The Federal Government strongly encourages all public and private sector employers, regardless of size, to plan for a pandemic, to protect the health of employees and assure continuity of operations."*

5. CDC SEES EARLY-SEASON SIGNS OF TAMIFLU RESISTANCE: *"With this year's US influenza epidemic barely getting started, there are already signs of increased viral resistance to oseltamivir (Tamiflu), the most widely used antiviral drug, the Centers for Disease Control and Prevention (CDC) said today."*

6. HETEROGENEOUS SELECTIVE PRESSURE ACTING ON INFLUENZA B VICTORIA- AND YAMAGATA-LIKE HEMAGGLUTININS: *"The detected amino acids are located at or near antigenic sites in influenza A virus H3 hemagglutinin."*

7. GRANZYME K EXPRESSING CYTOTOXIC T LYMPHOCYTES PROTECTS AGAINST INFLUENZA VIRUS IN GRANZYME AB(-/-) MICE: *"This suggests that grzK plays an*

important role in CD8(+) T-cell cytotoxicity both in the presence and absence of grzA and B."

CB Daily Report

Chem-Bio News

U.S. HHS SUPPORTS INTERCELL'S DEVELOPMENT OF VACCINE PATCH SYSTEM FOR PANDEMIC INFLUENZA
Intercell Press Release
December 10, 2008

"Intercell AG (VSE: ICLL) today announced the execution of a contract modification with the U.S. Department of Health and Human Services (HHS). The agreement commits additional funding of USD 12.5 m for Intercell's Pandemic Influenza program.

Intercell is developing a Pandemic Influenza Vaccine Patch System that includes an immunostimulant patch administered in conjunction with an injected Pandemic Influenza vaccine (manufactured by Solvay Biologicals, B.V., The Netherlands); the system is designed to enhance the immune response and enable dose sparing of the Pandemic Influenza vaccine.

The actual funding forms part of an HHS contract with potential funding of up to USD 128 m over five years. If successful, Intercell's Pandemic Influenza Vaccine Patch System would have the effect of expanding limited vaccine supplies by allowing fewer or lower doses of the vaccine.

The next Phase II study is expected to start in early 2009 and will be a randomized, blinded study to determine the optimal combination and dose of an injected H5N1 influenza vaccine and the vaccine patch from Intercell. The study will be conducted in the U.S. and is expected to enroll 500 subjects at six study sites."

The full article can be found at: http://www.intercell.com/ShowArticle.wa?seIDM=5879f19b-c8bb-4fd6-b612-18afd6ab63e6&seIDD=7D72E328-7FC2-44E4-B920-E7BAC033787A

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PROGRESS REPORTED AT WHO MEETING ON VIRUS SHARING
By Lisa Schnirring
CIDRAP News (Center for Infectious Disease Research & Policy – University of Minnesota)
December 15, 2008

"A World Health Organization (WHO) group that met last week in Geneva to solve problems related to global sharing of H5N1 avian influenza viruses made progress on language spelling out the commitment to sharing both the viruses and benefits, a senior US

government official told CIDRAP News.

The Intergovernmental Meeting on Pandemic Influenza Preparedness (IGM) wrapped up 6 days of sessions on Dec 13 with a plan to meet again just before or during the WHO's World Health Assembly in May 2009, according to the government official. The official, who requested anonymity, said the group still has several difficult issues to address.

Representatives from more than 100 countries participated in the negotiations, and the meeting was attended by a host of observers, nongovernmental organization representatives, and industry groups.

Topics for the next meeting will likely include difficult intellectual property (IP) issues related to virus-sharing and agreements on and mechanisms for sharing virus samples and ensuring benefits for countries that provide their viruses, the official said."

The full article can be found at: http://www.cidrap.umn.edu/cidrap/content/influenza/panflu/news/dec1508sharing-br.html

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GUIDANCE ON ANTIVIRAL DRUG USE DURING AN INFLUENZA PANDEMIC
AvianFlu.gov
December 15, 2008

"The use of prescription antiviral drugs to treat and prevent infection will be an important component of a pandemic influenza response. While current antiviral drug use strategies and publicly maintained stockpiles are targeted primarily for treatment of persons with pandemic illness, expanded antiviral drug production has allowed additional strategies to be considered. An interagency working group, with input from representatives of State, local and tribal public health agencies, considered scientific issues, ethics and values, and perspectives of stakeholders in developing draft guidance on antiviral use strategies and stockpiling. The antiviral drug use guidance in this document replaces the recommendations developed in 2005 which are published as part of the Department of Health and Human Service's (HHS's) pandemic influenza plan. As guidance, this document does not create a requirement; rather, it defines a prudent strategy for antiviral drug stockpiling and use that can contribute to a more effective pandemic response.

The guidance on antiviral use is based on the national pandemic response goals of slowing the spread of pandemic disease, reducing impacts on health, and minimizing societal and economic disruption. The working group recommends the following strategies and settings for antiviral use to meet these goals:

* Containing or suppressing initial pandemic outbreaks overseas and in the United States with treatment and post-exposure prophylaxis (PEP) among individuals identified as exposed to pandemic influenza and/or geographically targeted prophylaxis in areas where exposure may occur;
* Reducing introduction of infection into the United States early in an influenza pandemic

as part of a risk-based policy at U.S. borders[1];

* Treatment of persons with pandemic illness who present for care early during their illness and would benefit from such treatment;

* Prophylaxis of high-risk healthcare workers and emergency services personnel for the duration of community pandemic outbreaks;

* Post-exposure prophylaxis of workers in the healthcare and emergency services sectors who are not at high exposure risk, persons with compromised immune systems who are less likely to be protected by pandemic vaccination, and persons living in group settings such as nursing homes and prisons if a pandemic outbreak occurs at that facility."

The full article can be found at: http://pandemicflu.gov/vaccine/antiviral_use.html

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CONSIDERATIONS FOR ANTIVIRAL DRUG STOCKPILING BY EMPLOYERS IN PREPARATION FOR AN INFLUENZA PANDEMIC
AvianFlu.gov
December 15, 2008

"The Federal Government strongly encourages all public and private sector employers, regardless of size, to plan for a pandemic, to protect the health of employees and assure continuity of operations.[2] Influenza antiviral drugs (antivirals) are one of several approaches to protecting people during a pandemic and can serve as an important part of a layered approach to pandemic mitigation. In some cases, employees whose jobs would normally involve very high or high exposure risk to known/suspected pandemic patients may reduce or eliminate exposure through engineering, administrative and work practice strategies. Nonpharmaceutical measures and personal protective equipment should also be used as a critical component of an employer- ™s plan to protect employees during a pandemic. Employers that provide frontline healthcare and emergency services should plan to protect their employees who will be exposed to ill persons during a pandemic. This guidance recommends providing antiviral prophylaxis to these very high exposure risk and high exposure risk employees[3] for the duration of community pandemic outbreaks to prevent illness. Businesses that provide goods or services essential to community health, safety, or well-being have an obligation to plan and prepare for continued operations in the event of a pandemic. As a part of comprehensive pandemic planning, these critical infrastructure[4] employers should strongly consider providing antiviral prophylaxis for the small number of employees who are critical to essential operations. In addition, other employers may consider antiviral prophylaxis for workers in order to maintain business continuity.

If an employer is considering stockpiling antiviral drugs, it should do so with a clear understanding of the legal, regulatory, ethical, logistical, and economic issues that will be encountered in ordering, storing, securing and dispensing prescription medications. Employers should work with their company or contracted occupational health providers/ services to plan for stockpiling antivirals. This guidance does not establish the requirement or expectation that all employers stockpile antiviral drugs; rather, it defines a prudent strategy for employer antiviral drug stockpiling and use that can contribute to a more

effective pandemic response. Any employer that chooses to stockpile antivirals should do so as part of comprehensive pandemic preparedness and response activities in coordination with State and local pandemic preparedness plans and in conjunction with other measures to protect workers and maintain continuity of operations.

Antiviral drug stockpiles have been established at the Federal level and many States have also established stockpiles. Current recommendations focus on using up to 6 million courses of the Federally stockpiled antiviral drugs as part of a comprehensive public health response to contain the initial pandemic outbreak, wherever in the world it occurs, to reduce transmission when cases first appear in the United States, and to use the majority of stockpiled antiviral drugs to treat persons who have pandemic illness and may benefit from therapy.

Newly developed Federal guidance[5] recommends expanding antiviral drug use to include prophylaxis (i.e., antiviral use to prevent infection in persons either before or after they are exposed to pandemic influenza) in healthcare and emergency services occupations, for people whose immunity is compromised by an underlying medical condition or treatment, and for people living in group settings (e.g., nursing homes) if an outbreak of pandemic disease occurs at the facility. The Federal guidance on antiviral use also suggests a potential benefit of prophylaxis for workers who are critical to providing essential community services but leaves decisions on how to identify approaches to purchase and stockpile antiviral drugs to support its implementation to employers. Household contacts of ill persons also may benefit from prophylaxis.[6] However, further work is needed to assess the feasibility of stockpiling and providing antivirals for household contacts and to identify approaches to purchase and stockpiling the antiviral drugs to support its implementation. Despite expanding recommendations for antiviral drug use, there are no current plans for a commensurate expansion of public sector stockpiles and employers will have to take the lead role for protection of their workforce if these recommendations are to be implemented."

The full article can be found at: http://pandemicflu.gov/vaccine/antiviral_employers.html

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CDC SEES EARLY-SEASON SIGNS OF TAMIFLU RESISTANCE
By Robert Roos
CIDRAP News (Center for Infectious Disease Research & Policy – University of Minnesota)
December 12, 2008

"With this year's US influenza epidemic barely getting started, there are already signs of increased viral resistance to oseltamivir (Tamiflu), the most widely used antiviral drug, the Centers for Disease Control and Prevention (CDC) said today.

In its flu surveillance report for Nov 30 to Dec 6, released today, the CDC said 45 of 46 influenza A/H1N1 viruses tested so far have shown resistance to oseltamivir.

All the H1N1 viruses were susceptible to zanamivir (Relenza), the other antiviral drug in the

neuraminidase inhibitor class, the agency reported. All tested influenza A/H3N2 and B viruses were susceptible to both oseltamivir and zanamivir. Sixty-three percent of all the viruses tested came from only two states.

The CDC said all the H1N1 viruses also were susceptible to the adamantanes (amantadine and rimantadine), the older class of flu antivirals. However, 5 of 5 H3N2 viruses tested were resistant to the adamantanes (which do not work against type B viruses). The CDC has been recommending against using the adamantanes since January 2006 because of high resistance rates in H3N2 viruses."

The full article can be found at: http://www.cidrap.umn.edu/cidrap/content/influenza/general/news/dec1208cdc.html

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HETEROGENEOUS SELECTIVE PRESSURE ACTING ON INFLUENZA B VICTORIA- AND YAMAGATA-LIKE HEMAGGLUTININS
Drug Week
December 19, 2008

"As a consequence of immune pressure, influenza virus hemagglutinin presents some of its amino acids under positive selection. Several authors have reported the existence of influenza A hemagglutinin codons under positive selective pressure (PSP)."

"In this framework, the present work objectives were to demonstrate the presence of PSP and evaluate its effects on Victoria-and Yamagata-like influenza B viruses. Methodology adopted consisted in estimating the acceptance rate of nonsynonymous substitutions (omega=dN/dS) that describe the strength of selective pressure and identifying codons that may be positively selected, applying a set of continuous-time Markov chain codon-substitution models. Two groups of HA1 sequences (140 from Yamagata and 60 from Victoria lineage) were used. All the model maximum-likelihood estimates were obtained using codeml software application (PAML 3.15). The hypothesis of no existence of sites under PSP was rejected for both lineages ($p < 0.001$), using likelihood ratio tests. These results demonstrate the presence of positive selection acting on hemagglutinin of both Yamagata-and Victoria-like influenza B viruses. Several different sites were identified to be under PSP on Yamagata and Victoria hemagglutinins. Sites found with a posterior probability >0.95 were codons 197 and 199 in both lineages, codon 75 in the Yamagata lineage, and codon 129 in the Victoria lineage."

"The detected amino acids are located at or near antigenic sites in influenza A virus H3 hemagglutinin."

The full article can be found at: (B. Nunes, et. al., "Heterogeneous selective pressure acting on influenza B Victoria- and Yamagata-like hemagglutinins". Journal of Molecular Evolution, 2008;67(4):427-35). Link not available.

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GRANZYME K EXPRESSING CYTOTOXIC T LYMPHOCYTES PROTECTS AGAINST INFLUENZA VIRUS IN GRANZYME AB(-/-) MICE
Virus Weekly
December 16, 2008

"Granzyme (grz) AB(-/-) H2(b) mice generate numerically normal cytotoxic T lymphocyte (CTL) responses to the prominent influenza A virus (DNP366)-N-b and D(b)PA(224) epitopes and terminate the infectious process in the pneumonic lung with the same kinetics as the WT controls. Though grz B protein expression is fully compromised, there is only a partial effect on the level of CTL activity measured in a classical, short-term Cr-51 release assay," scientists in Cambridge, the United Kingdom report (see also Influenza).

"Single-cell polymerase chain reaction (PCR) analysis of both highly activated effector and ''resting'' memory CD8(+) T cells from influenza A virus-infected grzAB(-/-) mice showed a high prevalence of grzK mRNA(+) expression in tetramer (tet)(+) CTLs as was found in WT mice. However, a marked reduction in cytotoxicity present in the primary splenic CTLs of grzAB(-/-) mice correlated with decreased grzK expression, as measured by real-time PCR."

"This suggests that grzK plays an important role in CD8(+) T-cell cytotoxicity both in the presence and absence of grzA and B."

The full article can be found at: (M.R. Jenkins, et. al., "Granzyme K Expressing Cytotoxic T Lymphocytes Protects Against Influenza Virus in Granzyme AB(-/-) Mice". Viral Immunology, 2008;21(3):341-346). Link not available.

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